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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/001,863	11/19/2001	James G. Karras	ISPH-0618	1531

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 07/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/001,863	KARRAS ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *15-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-14 and 21-27* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11-19-01; 4-07-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-14, and SEQ ID NO: 25, in Paper No. 7 is acknowledged. The traversal is on the ground(s) that the restriction requirement should have been a species election. This is not found persuasive because, according to Applicants the particular oligonucleotide sequences set forth in claim 3 represent species that fall within the genus of claim 1. Furthermore, Applicants argue that each sequence recited in claim 3 hybridizes to the same mRNA and has the same function, i.e. to inhibit the expression of toll-like receptor 4.

First, Applicant's response is not complete, since it does not address the merits of the restriction between Groups I and II as set forth in the initial restriction requirement mailed 6-06-03. Applicants are merely arguing the further restriction of Group I to include a restriction of the nucleotide sequences as set forth in claim 3.

To reiterate the grounds for the restriction between invention groups I and II, as stated in the prior Office Action, Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the compounds of 8 to 50 nucleobases, and compositions thereof, can be used in methods for the detection of the presence of nucleic acid encoding Toll-like receptor 4 in cells or tissues. Moreover, because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their

different classification, restriction for examination purposes as indicated is proper. According to MPEP § 803, "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 808.02."

In regards to the question of whether the restriction of the oligonucleotide sequences set forth in claim 3 was proper, it is clear that a separate search and consideration of the prior art would be required for each oligonucleotide sequence set forth in claim 3. Moreover, the individual search of one of the oligonucleotide sequence set forth in claim 3 would not provide a sufficient search of the full scope of oligonucleotides encompassed by the broad genus of claim 1. It is noted that claim 1 is not limited to the nucleic acid sequence according to SEQ ID NO: 3, claim 1 encompasses all polymorphic and allelic variants of nucleic acid molecules encoding Toll like receptor 4. Any art identified by the search of one of the sequences set forth in claim 3 could not be used to identify all of the other nucleotide sequences set forth in claim 3. Furthermore, any art identified by the search of one individual nucleotide sequence set forth in claim 3, could not be used to either anticipate or render obvious all of the remaining sequence set forth in claim 3. If Applicants argue that the individual sequences are obvious over each other, then any art identified by the search of one sequence will be used in a rejection of the remaining sequences under 35 USC § 103(a).

It is clear from Applicant's own data that although the nucleotide sequences set forth in claim 3 are related to the extent that they target the same nucleic acid molecule encoding Toll-like receptor 4, each nucleotide sequence target different subsequences within the sequence according to SEQ ID NO: 3. Moreover, each individual sequence inhibits the expression of SEQ

ID NO: 3 in a separate and distinct manner. For example, according to Table 1, SEQ ID NO: 25 inhibits the expression of SEQ ID NO: 3 by 85%. However, for example, the oligonucleotide sequences of SEQ ID NO: 10, 11, 12, 16, 19, and 20, inhibit the expression of SEQ ID NO: 3 by 73%, 72%, 69%, 77%, 87%, and 83%, respectively. Each nucleotide sequence has a different effect on the level of inhibition of the expression of SEQ ID NO: 3. Moreover, each sequence has a distinct chemical structure, as evident by their distinct nucleotide sequences, and have distinct properties, as evident by their differential effect on the level of inhibition on Toll-like receptor 4 expression.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 15-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

3. In response to this Office Action must remove all reference to non-elected sequences set forth in claim 3, and non-elected target regions as set forth in claims 21-22 and 24.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-2 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Qureshi et al.

Qureshi et al. anticipate claims 1-2, and 11 by disclosing an oligonucleotide of 8 to 50 nucleobases in length targeted to nucleic acid encoding Toll like receptor 4 (TLR4), see page 617. For example, the following sequence is disclosed: 5' ACATGTCTAAAG-AGAGATTGAC, this sequence is "antisense" to nucleotides 517-538 of the nucleotide sequence encoding the Mus musculus TLR4 gene (See page 617, paragraph 6).

6. Claims 1-2, 4-6 and 11-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Lorenz et al. (WO 00/77204 A1).

Lorenz et al. anticipate claims 1-2, 4-6, and 11-12 by describing antisense oligonucleotides of 8 to 50 nucleobases in length targeted to nucleic acid encoding Toll like receptor 4. The oligonucleotides of Lorenz et al. may comprise modified nucleotides, modified sugars, and internucleotide linkages, see page 8, lines 20-32.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-2, 4-14, and 21-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lorenz et al. in view of Monia et al. (US Patent NO. 6,114,517), and Taylor et al.

The discussion of Lorenz et al. as set forth above is incorporated here. However, Lorenz et al. does not teach the chimeric oligonucleotides, specific sugar and nucleobase modifications, or the colloidal dispersion system composition claimed by Applicants. Additionally, Lorenz et

al. does not teach the design of antisense oligonucleotides specifically hybridizable to the start or stop region, the coding region, the 5'UTR or the 3' UTR. Moreover, Lorenz et al. does not teach antisense oligonucleotides that inhibit Toll-like receptor 4 by at least 50% or 70%.

Monia et al. teach that the design of antisense oligonucleotides comprising various modifications, including phosphorothioate modified internucleoside linkages (col. 8, line 41-43), 2'-O-methoxyethyl sugar modifications (col. 10, line5), 5-methylcytosine modified nucleobase (col. 10, line 31-32), and wherein the antisense oligonucleotide is a chimeric oligonucleotide (col. 11, line 51). The modified or substituted oligonucleotides of Monia et al. are preferred over native (unmodified or unsubstituted) forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced binding to target and increased stability in the presence of nucleases (col. 8, lines 2-6).

The antisense oligonucleotides of Monia et al. are preferably designed to target the following regions of an mRNA: the coding region, the 5' untranslated region (5'UTR), 3' untranslated region (3'UTR), and the translation initiation (start region) and the translation termination regions (stop region), see col. 5-6).

Additionally, Monia et al. teach the use compositions comprising antisense oligonucleotides and a pharmaceutically acceptable carrier or diluent, and further comprising a colloidal dispersion system in order to enhance the stability of oligonucleotides introduced into cells and to target oligonucleotides to a particular tissue or cell (col. 15, lines 19-41).

It would have been obvious to one of ordinary skill in the art, at the time of the instant invention, to modify the teachings of Lorenz et al. with the teachings of Monia et al. in the design of the antisense compounds according to the present invention and the composition

according to present invention comprising pharmaceutically acceptable carrier or diluent, and further comprising a colloidal dispersion system. One of ordinary skill in the art would have been motivated to make this modification because Monia et al. teach that antisense compound modified according to the present invention and compositions designed according to the present invention would enhance the stability of oligonucleotides introduced into cells and would help to target oligonucleotides to a particular tissue or cell.

Additionally, in regards to wherein the antisense compounds of the present invention must reduce the expression of Toll-like receptor 4 (TLR4) mRNA by at least 50% or 70%, according to Taylor et al. (December 1999), one of skill in the art at the time the instant invention was made, using high affinity chimeric oligomers and a bioinformatics program to select accessible sites, would only need to screen 3-6 oligomers per target gene to find one that inhibits a gene with 66-95% efficiency. Absent evidence to the contrary the antisense compounds designed according to the teachings of Lorenz et al. in view of Monia et al., would inherently possess the same functional activity as Applicant's claimed compounds.

Therefore, the invention as a whole, at the time of the instant invention, would have been *prima facie* obvious of Lorenz et al. in view of Monia et al. and Taylor et al.

9. Claims 1-2, 4-14, and 21-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

10. The instant claims are drawn to a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding Toll-like receptor 4 (TLR4), wherein said compound specifically hybridizes with said nucleic acid molecule encoding Toll-like receptor 4 and inhibits the expression of Toll-like receptor 4. The specification as filed describes the structures of compounds targeting human TLR4 according to SEQ ID NO: 3. However, Applicant's specification does not provide an adequate description of all of the embodiments encompassed by the compounds of claim 1. According to the specification as filed, page 9, an antisense compound is "specifically hybridizable when binding of the compound to the target DNA or RNA molecule interferes with the normal function of the target DNA or RNA to cause a loss of utility, and there is a sufficient degree of complementarity to avoid non-specific binding of the antisense compound to non-target sequences under conditions which specific binding is desired, i.e., under physiological conditions in the case of *in vivo* assays...." Additionally, it is stated that "[I]t is understood in the art that the sequence of an antisense compound need not be 100% complementary to that of its target nucleic acid to be specifically hybridizable." Therefore, the instant claims encompass compounds of 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding TLR4, including all forms of TLR4 nucleic acid isolated from all sources, including all polymorphic, allelic and splice variants of this nucleic acid. Moreover, in order for the claimed compound to "specifically hybridize" to all forms of nucleic acid encoding TLR4, wherein said compound is of sufficient complementarity to all forms of TLR4, avoid non-specific binding to other sequences, and interfere with the normal function of the target nucleic acid sequence, the skilled artisan would have to know the structure of all forms of nucleic acid encoding TLR4 in order to design the compounds of the present invention. Applicants provide

only a description of compounds according to the present invention which target nucleic acid encoding human TLR4 according to SEQ ID NO: 3.

The compounds according to the present invention which target SEQ ID NO: 3 can not be used to predict the structures of compounds which would be effective to "specifically hybridize" to forms of TLR4 isolated from other organisms since functional antisense compounds can only be identified empirically.

See the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement (Vol. 66, No. 4, pages 1099-1111). These guidelines state that: "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

Additionally, MPEP § 2163 [R-1] states "The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only

by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

Applicant's specification does not provide a sufficient description of all embodiments encompassed by the claimed compounds, which would allow one of skill in the art to predict the structures of all members of the claimed genus of compounds. Moreover, it is apparent that further experimentation is required to identify the structures of all embodiments encompassed by the instant claims. Therefore, the specification does not describe the claimed compounds in such full and concise terms so as to indicate that the applicant had possession of the full scope of compounds encompassed by the instant claims at the time of filing of this application.

Claim Objections

11. Claim 3 is objected to because Applicants have not amended the claim to remove all reference to non-elected subject matter. However, no prior art reference has been identified which discloses the elected invention of an antisense oligonucleotide of 8 to 50 nucleobases in length comprising SEQ ID NO: 25.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Janet L. Epps-Ford, Ph.D.
Patent Examiner
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JLE